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Review

Complement in systemic lupus erythematosus across time and space: from tolerance to tissue injury and from extracellular to intracellular functions[☆]

Giovanna Clavarino¹, Jeanne Vigne², Marie-Sophie Meuleman³, Axelle Amen¹, Véronique Rossi² and Chantal Dumestre-Pérard¹

The complement system plays a paradoxical role in systemic lupus erythematosus physiopathology, acting both as a protective mechanism and as a driver of tissue injury, depending on disease stage. Neutrophil extracellular traps (NETs) further exacerbate disease activity by promoting complement activation and autoantigen exposure, forming an amplifying inflammatory loop. Lupus nephritis remains challenging to monitor using conventional complement biomarkers such as CH50, C3, and C4; the utility of anti-C1q, anti-ficolin, and anti-C1s antibodies, along with tissue-based markers such as renal C4d and C5b-9 deposits, as markers of disease activity and prognosis, is discussed. Interestingly, noncanonical functions of complement, including intracellular roles in immune cell metabolism regulation, have been recently described. Understanding the crosstalk between complement, NETs, and immune metabolism may provide new targets for therapeutic intervention.

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease in which dysregulated innate and adaptive immunity converge to drive organ damage, most prominently in the kidney. The complement system occupies a central, and paradoxical, position in this process. Classical pathway components such as C1q and C3 facilitate immune tolerance by clearing apoptotic debris and immune complexes (ICs); however, complement activation also generates anaphylatoxins and the membrane attack complex that propagate inflammation and tissue injury. Genetic deficiencies in early classical pathway proteins strongly predispose to SLE, underscoring the protective role of complement, while hyperactivation increases disease activity. Beyond extracellular effector functions, noncanonical and intracellular complement, the complosome, regulates immune-cell metabolism, shaping macrophage polarization and T-cell effector activation. Neutrophil extracellular traps (NETs) contribute to a self-amplifying inflammatory loop, since NETs expose autoantigens and provide a scaffold for complement activation, while complement fragments promote NETosis. In lupus nephritis (LN), standard immunological biomarkers (CH50, C3, C4, anti-dsDNA autoantibodies) may lack sensitivity and specificity, prompting interest in other serologic markers (anti-C1q, anti-ficolin, and anti-C1s autoantibodies), cell-bound activation products, and tissue deposits (C4d, C5b-9) that might better reflect intrarenal complement activity and disease prognosis. This review synthesizes current evidence on the temporal duality of complement in SLE, its crosstalk with NETs and immune metabolism, and the evolving repertoire of circulating and tissue biomarkers to refine disease monitoring and illuminate new therapeutic targets.

Dual role of complement in systemic lupus erythematosus: a matter of time

SLE is a chronic and systemic relapsing–remitting autoimmune disease characterized by dysregulated immune responses leading to inflammation and damage in different organs. Defective clearance of

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apoptotic cells leads to the accumulation of self-nuclear antigens. Upon autoantigen and danger signal recognition, innate immune responses are responsible for high type I IFN production, especially by plasmacytoid dendritic cells (pDCs), which orchestrates the immune response with the activation of adaptive immunity and finally autoantibody production [1,2]. The antibody-antigen ICs deposited in tissues activate complement, with membrane attack complex formation and anaphylatoxins C3a and C5a production, finally triggering inflammation and multiorgan failure [3]. Moreover, complement receptor-dependent pathways implicating CR3, CR4, and CD21 (CR2) increase the pathogenic process by facilitating antigen processing and presentation by dendritic cells and B-cell response [4,5].

The complement system plays a major role in SLE pathophysiology; however, its role is complex since it may both prevent and exacerbate the disease [4]. The duality of the role of complement in SLE and especially of its classical pathway is of particular interest and well illustrated by the protective effects of C1q and C3b for the clearance of apoptotic bodies and the elimination of the circulation of ICs, and by the roles of complement in inflammation. Hyperactivated complement system may lead to excessive inflammation and tissue damage, while hypoactivation of complement may impair the clearance of apoptotic debris and ICs, thereby promoting autoimmunity. Patients with hereditary deficiencies in classical pathway complement proteins (C1q, C2, C4) have a high risk of developing SLE [6]. Activation of the classical pathway leads to the consumption of circulating C3 and C4 proteins, since they deposit in tissues such as kidneys. Therefore, complement contributes to lupus inflammation, but its deficiency triggers lupus: this complement ‘paradox’ in SLE has been recently reviewed by Pickering and Botto [7], as well as the ‘canonical’ and ‘noncanonical’ functions of complement.

The expression ‘noncanonical’ is used to indicate complement roles, particularly those mediated by C1q, that do not lead to the activation of the complement system. Interestingly, it has been proposed that C1q might have dual roles according to disease stage: C1q plays a protective role in early disease when, together with C3, it contributes to maintaining tolerance by facilitating autoantigen clearance, while in later stages, C1q recognition of ICs and subsequent classical complement pathway activation exacerbates tissue inflammation and disease progression [7] (Figure 1).

Independent of its role in complement activation, a number of protective interactions of C1q with phagocytes have been observed, triggering phagocytosis of cellular debris and polarizing macrophages toward an

anti-inflammatory phenotype. Indeed, the site responsible for C1q interaction with phagocytes has been shown to be independent of the C1r₂C1s₂ interaction site, which is instead important for complement activation [8]. Autoantibodies against C1q bind to ligand-bound, solid-phase C1q and not to fluid-phase C1q, as recently described in Dijkstra et al. [9]. In this study, a fine characterization of these autoantibodies pointed out that they recognize the collagen-like region of C1q when C1q is in complex with a range of its natural ligands, such as antigen-bound IgG, IgM, CRP, or necrotic cells, and can activate immune cells through Fc-receptor engagement, thus contributing to disease pathogenesis.

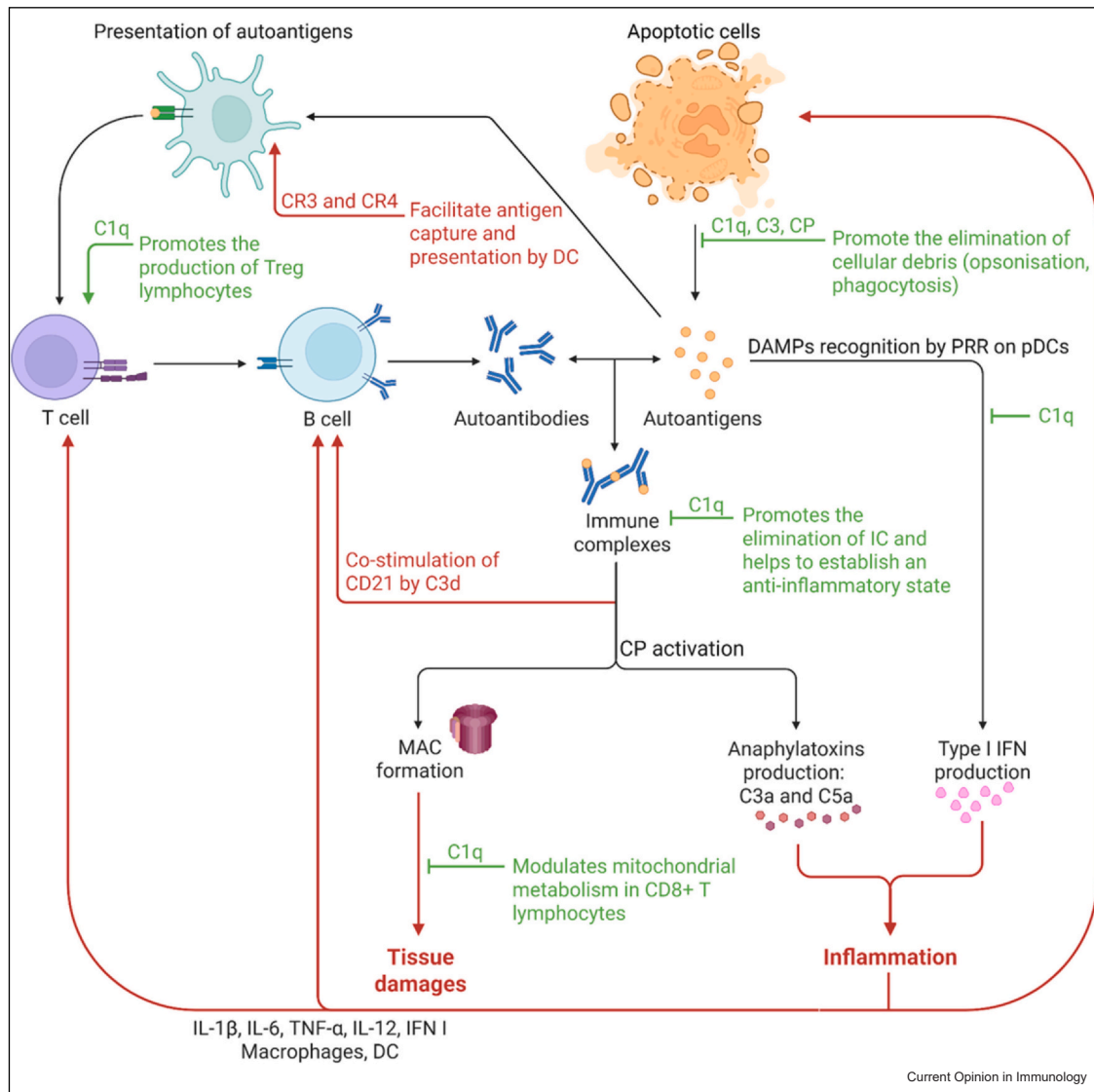
The crosstalk between neutrophil extracellular traps and complement in SLE as an inflammatory feedback loop

The crosstalk between NETs and complement cascade has been recently described, leading to the amplification of tissue inflammation: complement activation can lead to NET formation and conversely, NETs can amplify complement-mediated tissue damage [10,11] (Figure 2).

NETs have been described as a mechanism of entrapping and killing pathogens through a regulated form of neutrophil cell death: upon activation, neutrophils can release chromatin together with antimicrobial peptides and enzymes [12]. Among other enzymes, activation of the nicotinamide adenine dinucleotide phosphate oxidase complex leads to the release of neutrophil elastase and myeloperoxidase from cytoplasmic granules, then elastase induces histone degradation, leading to DNA decondensation and release of NETs outside the cells. Circulating NETs are finally degraded mainly by plasma DNase I and ultimately removed by macrophages. Of note, NET formation independently of nicotinamide adenine dinucleotide phosphate oxidase complex activation has also been described [13].

Interactions between complement components and NETs in autoimmune diseases affecting the kidneys, such as SLE, have been pointed out. Once activated, neutrophils can release complement factors of the alternative pathway (AP), such as Factor B and properdin. Through an autocrine mechanism, properdin deposits on the neutrophil membrane, triggering the cleavage of C3 and complement activation, leading to neutrophil lysis with consequent NETosis. Furthermore, on the neutrophil membrane, complement activation may be controlled by Factor H, an inhibitor of AP [14]. Neutrophil granule proteins, such as myeloperoxidase, have been shown to be able to cleave C5 into active fragments [15], while cathepsin G and neutrophil elastase can cleave C3 [16]. Moreover, properdin, Factor B, and C3 have been

Figure 1

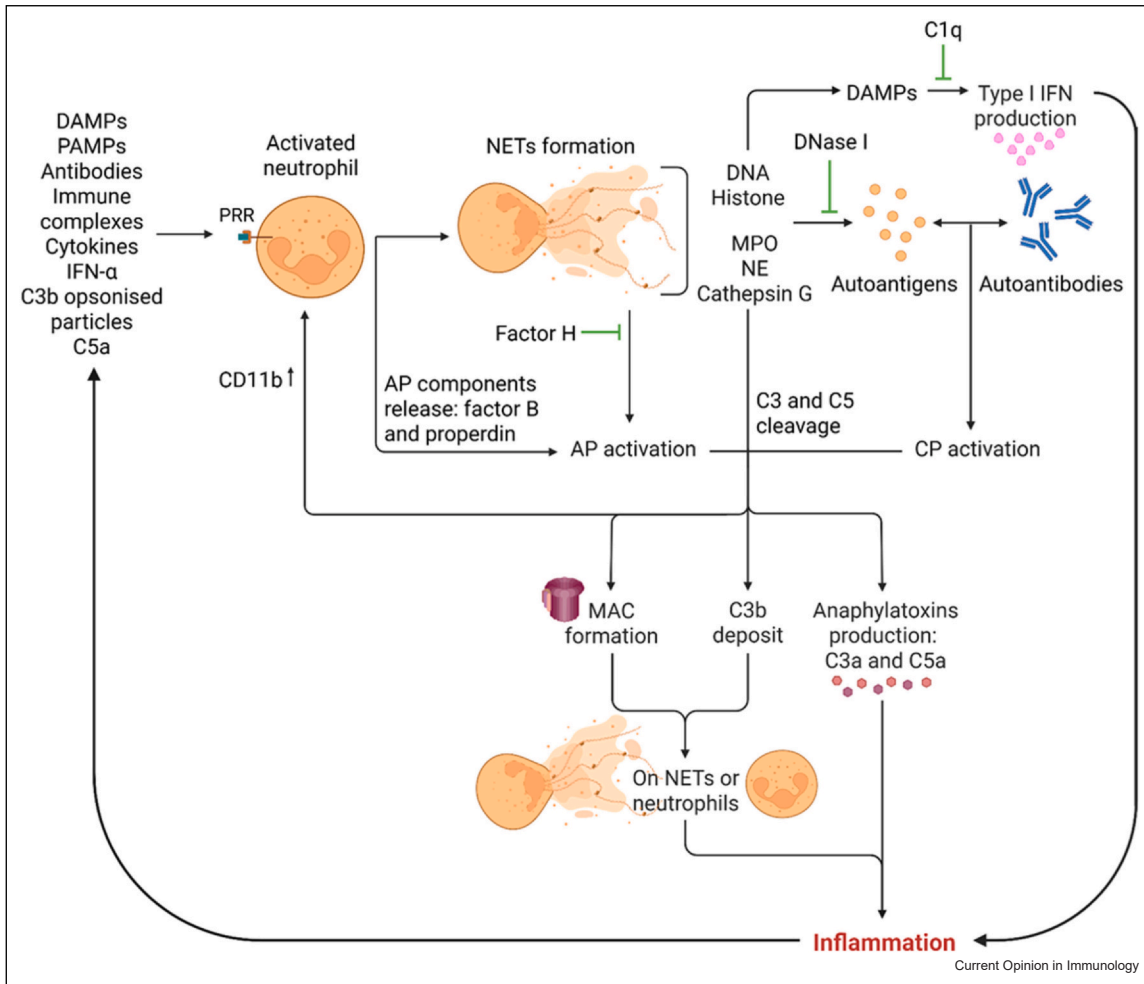


Dual role of complement in SLE pathophysiology. The complement system performs both protective (in green) and pathogenic (in red) functions in SLE. Complement components, notably C1q, C3, and the classical pathway (CP), promote the clearance of apoptotic debris and immune complexes (ICs), thereby limiting exposure to autoantigens. C1q plays an essential role in contributing to the establishment of an anti-inflammatory state, the induction of regulatory T cells (Tregs), and the modulation of the mitochondrial metabolism of CD8+ T cells. Activation of the CP leads to the formation of the membrane attack complex (MAC) and the release of anaphylatoxins (C3a, C5a), contributing to tissue damage and inflammation. The recognition of DAMPs by plasmacytoid dendritic cells (pDCs) contributes to the onset of inflammation by inducing the secretion of type I IFN. Complement receptor-dependent pathways (CR3, CR4) and CD21 (CR2) reinforce these pathogenic processes by promoting the presentation of autoantigens by dendritic cells (DCs) and the B response. *Created with Biorender.com.*

found to be deposited on NETs; thus, complement activation occurs not only on neutrophil membranes but also on released NETs. Factor H is also recruited on NETs to counteract C3b activation. The balance between NET release and removal is crucial, since impaired clearance can increase immune responses against DNA, histones, and intracellular proteins associated with NETs [17,18].

Important amounts of NETs are found in the kidneys, skin, and blood of SLE patients, and their presence is associated with disease activity [19]. Moreover, SLE patients have an impaired ability to degrade NETs via DNase [20]. Circulating autoantibodies, such as anti-dsDNA, targeting NET components, form ICs that activate pDCs and induce type I IFN production via TLR7 and TLR9 pathways; type I IFN promotes

Figure 2



Crosstalk between complement and NETs as a positive feedback loop in SLE inflammation. Neutrophils activated by various stimuli (DAMPs, antibodies, immune complexes, C5a, etc.) are able of releasing neutrophil extracellular traps (NETs) rich in DNA, histones, myeloperoxidase (MPO), neutrophil elastase (NE), and cathepsin G. If not degraded (in the absence of DNase I, for example), these components can constitute autoantigens and thus activate complement via the classical (CP) and alternative (AP) pathways. Neutrophil activation can induce the secretion of Factor B and properdin, leading to AP activation, which can be inhibited by Factor H. MPO, NE, and cathepsin G are also capable of cleaving C3 or C5, contributing to general complement activation. The formation of the membrane attack complex, the deposition of C3b, the production of anaphylatoxins (C3a and C5a), and the resulting increase in CD11b reinforce the recruitment and activation of neutrophils, maintaining an inflammatory feedback loop. The presence of DNA and histone in the extracellular environment also induces the production of type I IFN, contributing to the general inflammatory state. Created with Biorender.com.

immune cell activation and further NET formation [21]. Impaired NET clearance is an important pathogenic mechanism in SLE, associated with lower serum C3 and C4 levels and higher susceptibility to glomerulonephritis in patients with elevated NET levels [22].

Understanding the crosstalk between complement and NETs in renal involvement in autoimmune diseases is a new challenge for developing specific therapeutic strategies that modulate either NET production (e.g. PAD4 inhibitors) or NET removal (e.g. recombinant DNase I), both

of which are in phase I-II clinical trials for SLE and (anti-neutrophil cytoplasmic antibody)-associated vasculitis [10].

Lupus nephritis: an update on biomarkers in serum and in tissues

Serum concentrations of complement proteins of the classical pathway, such as C3 and C4, serve as circulating biomarkers for SLE activity, as well as CH50 (Complement Haemolytic 50); these parameters are part of the SLEDAI (SLE Disease Activity Score), which is routinely used in clinical practice.

LN is one of the most severe and frequent SLE involvements. Early diagnosis of lupus renal flare is a challenge in SLE management and is crucial for the appropriate treatment of patients. Proteinuria and creatinine clearance are conventional markers for the evaluation of renal activity, while low levels of C3 and C4 and high titers of anti-dsDNA antibodies are immunological biomarkers related to inflammation level [23,24]. Nevertheless, these parameters often lack sensitivity and specificity for detecting lupus renal flare, thus pointing out the need for novel biomarkers for LN diagnosis and prognosis.

Pathogenic role of autoantibodies against serum protective molecules involved in the uptake of dying cells, such as C1q, mannose-binding lectin, pentraxins, and ficolins has been well reviewed by Dumestre-Pérard et al. [25]. These proteins bind to apoptotic cell-associated molecular patterns and facilitate phagocytosis of the opsonized cells by interacting with phagocyte receptors and leading to an anti-inflammatory response. Several studies agree that anti-C1q antibodies have a high negative predictive value for active LN. Interestingly, they decrease significantly with clinical improvement under treatment [26,27]. Compared to nonproliferative forms, proliferative ones (class III and class IV) are frequently associated with challenging outcomes. A recent study pointed out that high titers of anti-C1q antibodies and a high number of erythrocytes in urinary sediment have high negative predictive values for proliferative LN, with the persistence of anti-C1q antibodies after one year of therapy being significantly associated with the risk of renal flares [28].

Ficolins (ficolin-1, -2, and -3) are lectin-like innate immune recognition proteins able to trigger activation of the lectin complement pathway. They are part of the defense collagens family, and they mediate immune effector functions similar to C1q. Anti-ficolins antibodies have been detected in SLE patients with active LN. We suggested that the combination of anti-C1q, anti-ficolin-2, and anti-ficolin-3 antibodies could be interesting as a multi-marker panel for LN evaluation [29]. The serine protease C1s is crucial in the complement cascade since, upon activation of C1r and C1s by C1q, C1s cleaves C2 and C4 to form the C3 convertase. Recently, it has been described that patients with LN showed significantly higher levels of anti-C1s antibodies than SLE patients with other flare types. Anti-C1s antibodies recognized mainly the C1s N-terminal part, which is essential for the formation of the C1₂C1s₂ tetramer and therefore for the activation of proenzyme C1s [30].

Cell-bound complement activation products, such as C3b, C4b, and C4d, form covalent bonds that deposit irreversibly on the cell membranes of various cell

types, such as erythrocytes, B cells, and T cells, reflecting sustained complement activation. Anti-C4 and especially anti-C3b autoantibodies have been shown to be strongly correlated with LN and have high predictive value for future flares [31]. T cell-bound C4d has recently been described as an interesting biomarker, especially in SLE-specific autoantibody-negative patients with normal complement [32]. Terminal complement complex C5b-9 has been shown to correlate with lupus flares and is thus useful for monitoring lupus activity [33].

A model of eight endotypes of SLE, developed with machine learning algorithms, was recently validated based on whole-blood expression gene profiles, with low levels of C3 and C4 clustering in the same endotype enriched for a plasma-cell and interferon-stimulated gene signature [34]. Clustering SLE patients based on transcriptional profiles and clinical outcomes may provide novel molecular insights in support of personalized treatment.

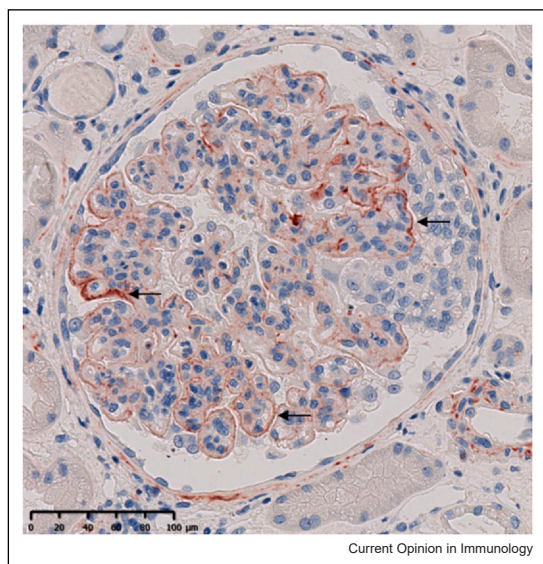
In addition to fluid-phase biomarkers, several studies have examined the presence of complement protein deposits within renal tissue in the context of LN. In addition to being necessary for LN diagnosis, these tissue-based biomarkers may hold potential for identifying the most severe forms of the disease or those associated with poorer prognoses.

Most studies have focused on intrarenal C4d deposits. The vast majority of kidneys affected by LN show C4d deposits. These latter are primarily located in the glomerular compartment, and less frequently in peritubular capillaries or the tubular basement membrane [35–40]. Two independent studies have reported a strong correlation between the intensity of glomerular C4d deposits and the presence of glomerular microthrombi [38,40]. While the prevalence of peritubular capillary C4d deposits varies between studies, several articles have identified a correlation between these deposits and the clinical, histological, and immunological activity of the disease [35–37].

The specific characterization of intrarenal activation of the AP has been explored in a few studies [41,42]. One study suggested that, unlike an ‘alternative pathway’ profile (C3 deposits without C4/C1q), the ‘classical pathway’ profile (combination of C3/C4/C1q deposits) is associated with a more immunologically active disease, a better response to immunosuppressive treatment, and a better renal prognosis [42].

In addition, a few studies have proposed investigating intrarenal activation of the terminal pathway through analysis of renal C5b-9 deposits (example given in Figure 3). Depending on the study, between half and all

Figure 3



Histopathological renal lesions and C5b-9 deposits in lupus nephritis. Representative example of C5b-9 immunolabeling (dark arrows) in renal tissue from a patient with class IV lupus nephritis (x20).

LN kidneys are positive for significant C5b-9 deposits [43,44]. Of note, these two articles differ in the detection antibodies and in the deposit quantification methods used. However, both studies agree in identifying a correlation between the extent of C5b-9 deposits and a poorer response to immunosuppressive treatment, without an association with the histological activity of the disease. Finally, it appears that the extent of tubular C5b-9 deposits correlates with the severity of chronic interstitial histological lesions (interstitial fibrosis and tubular atrophy) [45].

Overall, current investigations have most often been limited to the analysis of a single or few tissue biomarker (s), and to date, no study has conducted a comprehensive assessment of intrarenal activation across the various complement pathways. There appears to be a link between the intrarenal complement activation profile and the histological, clinical, and immunological presentation of the disease, which would warrant further investigation.

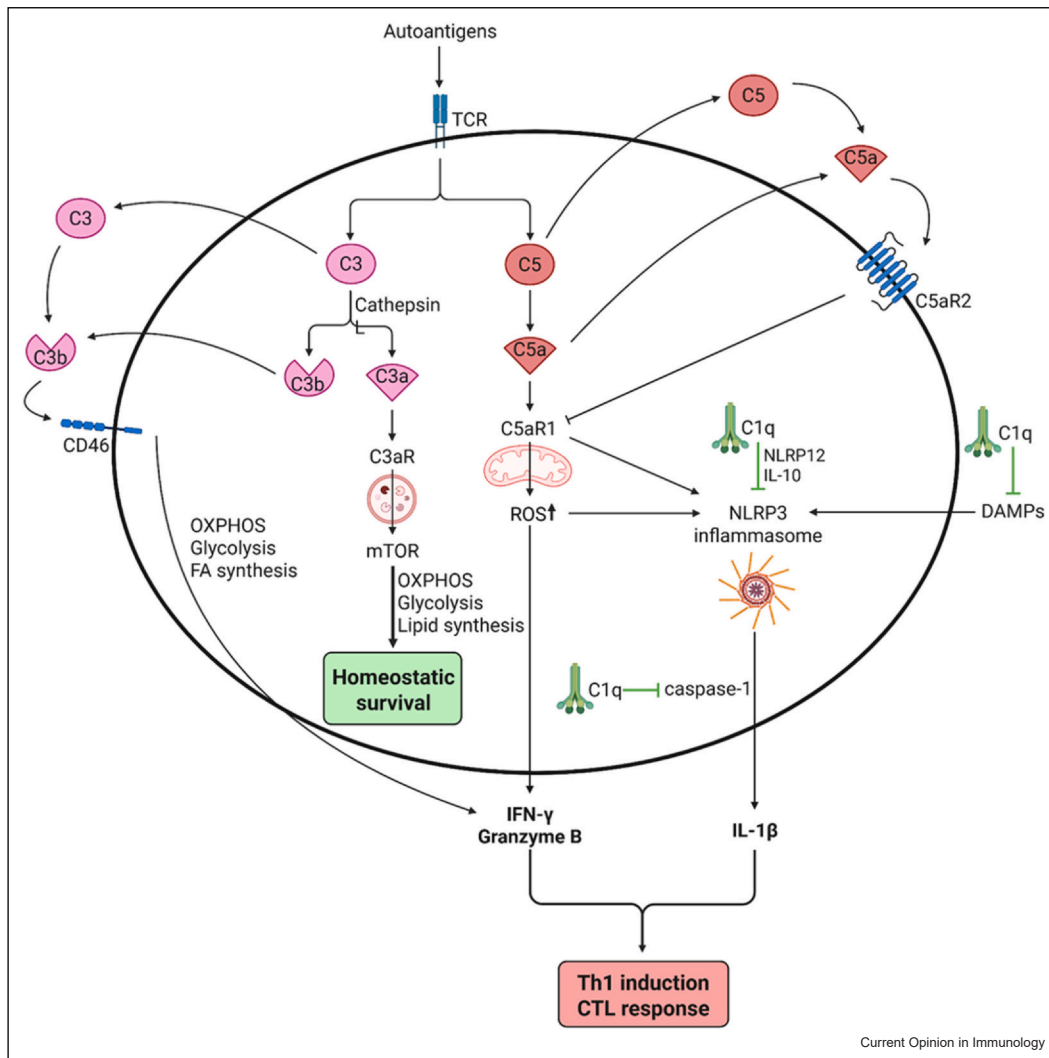
Intracellular complement and metabolism: a bridge between innate and adaptive response

Interestingly, in recent years, complement activation and functions have been shown to occur not only in the extracellular compartment but also within cells. Complement activation regulates key metabolic pathways with an effect on cellular processes such as survival, proliferation, and differentiation [46]. Complement can negatively regulate NLRP3 (NLR family

Pyrin domain containing 3) inflammasome, with C1q suppressing caspase-1 cleavage and subsequent mature IL-1 β production in macrophages during phagocytosis of apoptotic cells, while also inducing IL-10 secretion. Thus, by directly regulating NLRP3 inflammasome, C1q can limit its excessive activation triggered by DAMPs (damage-associated molecular patterns) [47]. In a recent review by West et al. [48], the intracellular complement, named as ‘composome’, has been pointed out as a central orchestrator of normal cell physiology, with a major role in T cell effector and contraction phases. Intracellular C3 in T cells provides a homeostatic survival signal via constitutive mechanistic target of rapamycin activation. Moreover, antigen binding via the T cell receptor induces the shuttling of intracellularly generated C3b to the T cell surface. There, C3b engages CD46, leading to the metabolic reprogramming toward glycolysis and oxidative phosphorylation necessary for IFN γ production and Th1 induction, or granzyme B expression and CD8⁺ cytotoxicity function (Figure 4). The implication of complement proteins in cleaving cytotoxic granules within T cells, leading to their activation, has also been described [49].

Among noncanonical functions of C1q, it has been described that in an inducible model of SLE, once tolerance is broken, C1q is required to restrain immune response to self-antigens and that this effect is mediated by CD8⁺ T cells [50]. During the propagation of the autoimmune process, this novel C1q-mediated function allows regulating the effector CD8⁺ T cells via the p32/gC1q receptor and the modulation of the mitochondrial metabolism of these cells, independently of complement cascade activation. Cytotoxic T cells contribute to amplifying tissue injury, since periglomerular CD8⁺ T-cell infiltration is associated with poor prognosis in patients with active LN [51]. Metabolic abnormalities in CD8⁺ T cells from lupus patients, due to type I IFN signaling, have been observed, increasing the susceptibility of these cells to undergo apoptosis. By using high-throughput RNA sequencing in T cells from SLE patients, a link between type I IFN signature and mitochondrial changes in CD8⁺ T cells has been pointed out: these metabolic abnormalities are the result of prolonged type I IFN exposure together with T cell receptor stimulation by autoantigens. These two stimuli enhance the consumption of NAD⁺, increasing reactive oxygen species production and altering the morphology and function of the mitochondria in CD8⁺ T cells, making them prone to die. Thus, upon increased energy demand, such as in response to antigen challenge or stress, type I IFN-stimulated CD8⁺ T cells are more susceptible to undergo apoptosis, exacerbating ongoing autoimmunity by increasing exposure to self-antigens [52].

Figure 4



Intracellular complement orientates T cell activation and differentiation. Activation of TCR induces the production of C3 and C5, which can be secreted or cleaved intracellularly by cathepsin L for C3 and by an unknown protease for C5. The resulting intracellular C3a can interact with lysosomal C3aR to activate the mTOR pathway, thereby promoting homeostatic survival by modulating cellular metabolism such as oxidative phosphorylation (OXPHOS). C3b can be secreted and interacts with the surface receptor CD46. Its activation modulates glycolysis and fatty acid (FA) synthesis, inducing the secretion of IFN- γ and granzyme B in CD8⁺ lymphocytes. The formation of intracellular C5a affects oxygen metabolism and induces an increase in the production of reactive oxygen species via the mitochondrial receptor C5aR1. This signaling contributes to the production of IFN- γ and granzyme B and to the assembly of the NLRP3 inflammasome, whose activation can be initiated by other stimuli such as DAMPs. The NLRP3 inflammasome induces the secretion of IL-1 β , which, in addition to IFN- γ and granzyme B, participates in the induction of Th1 and cytotoxic (CTL) responses. C1q exerts a negative regulatory role on this proinflammatory cascade by sequestering DAMPs and inhibiting the activation of the NLRP3 inflammasome and caspase-1 (green arrows). *Created with Biorender.com.*

Conclusion

In conclusion, serum-circulating complement is critical for its sentinel function in the recognition and removal of pathogens breaching host barriers; autocrine-functioning complement directs T cell and antigen-presenting cell responses, and intracellular complement is now recognized as a critical regulator of cell physiology. Therefore, it seems that ancient pathogen-sensing

systems, such as complement, are also the heart of cell homeostasis, activation, and function via the induction of metabolic changes. Since the complement can regulate cell metabolism, it has been suggested that complement could have functioned originally as an intracellular sensor system. Later, with the evolution of life from unicellular to multicellular and multiorgan organisms, it became a secreted and systemic system; therefore, PRR

(Pattern Recognition Receptors) may have primarily evolved as sensors of metabolic changes and only then as protection against infections [53]. These considerations suggest that the role of the complement system in autoimmune diseases should be reevaluated and that a better understanding of the mechanisms underlying these ‘new’ roles of complement may give a foundation for novel therapeutic strategies.

Declaration of Competing Interest

The authors declare no conflict of interest.

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